Cerebral Vasomotor Reactivity, Functional TCD and Cerebral Autoregulation

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Functional sonographic imaging

- **Investigations of the global cerebral vasoreactivity using *unspecific stimuli***

  (changes of arterial blood pressure during testing of autoregulation, changes of blood CO₂ in apnea test and during hyperventilation).

- **Investigations of cerebral hemodynamics using *specific stimuli***

  (FV changes of the PCA during visual stimulation, FV changes of the MCA during cognitive stimulation).
Physiological Regulations of Cerebral Hemodynamics

MCA and sequential arterioles in different functional states

Normal TCD recording of MCA

MFV = 52 cm/s

\[ R = \frac{S-D}{S} = 0.56 \]

diameter of MCA normal
diameter of arterioles normal
diameter of MCA normal
diameter of arterioles dilated

MFV ↑ R ↓ Pulsatility ↓

diameter of MCA normal
diameter of arterioles reduced

MFV ↓ R ↑ Pulsatility ↑
PHYSIOLOGICAL REGULATIONS OF CEREBRAL HEMODYNAMICS

II  endexspiratory hypercapnia → apnea

MFV and Pourcelot-Index (R) in different functional states

III  hypocapnia → hyperventilation

MCA and sequential arterioles in different functional states

diameter of MCA normal

diameter of arterioles dilatated

diameter of MCA normal

diameter of arterioles reduced
Normal vasomotor reactivity

Exhausted vasomotor reactivity
**CO₂ – STIMULATION**

- CO₂ concentration in normal inspiratory air is about 0.03%
- 5% CO₂ in the inspiratory air increases the pCO₂ by about 8 mmHg
- Carbogen-gas → fixed mixture of 5% CO₂ in 95% O₂
- A closed system for breathing is necessary; pure rebreathing needs too much stimulation time to reach a sufficient CO₂ increase.
- The most suitable condition between stimulation time and CO₂ increase can be reached providing the patient with carbogen-gas in a closed system.
PERFORMING THE CO₂-TEST

• During CO₂ stimulation or reduction of CO₂ → patient should be lying or sitting comfortably.

• A mask is placed at the patient’s face.

• Recordings of MCA’s FV by simultaneous measurement of end-tidal CO₂ concentration (CO₂ analyzer), BP and HR.

• After reaching a steady state in MCA’s FV and end-tidal CO₂ values → air with CO₂ concentrations of 5% should be given for 2-3 min until steady state is being reached again.

• The same should be done for hyperventilation.
VMR = \frac{FV_{hyper} - FV_{rest}}{FV_{rest} \times (pCO_{hyper} - pCO_{rest})} \times 100 \quad [\% / \text{mmHg}]

VMR = 100 \times \frac{85 - 52}{52 \times (41 - 30)} = 5.77 \% / \text{mmHg}
FINDINGS IN NORMAL VOLUNTEERS

Study I: VMR: Tangent
hyperbolic function

40 healthy adults (20 to 75 years)
MCA both sides
Calculated VMR → 86 ± 16 [%]

(Ringelstein et al. 1988)

Study II: VMR: Linear
function

15 healthy adults (18 to 63 years)
MCA, ACA, PCA both sides
Calculated VMR → 5.26 ± 1.61 [%/mmHg]

(Diehl et al. 1994)
FINDINGS IN PATIENTS

Three stages of a disturbed VMR can be differentiated:

1. rel. reduction of VMR: side difference more than 3%/mmHg or 2%/mmHg < VMR < 5%/mmHg

2. restricted VMR: VMR < 2%/mmHg

3. exhausted VMR: VMR < 1%/mmHg
VMR IN A PATIENT WITH RIGHT ICA OCCLUSION

- Reduced VMR of the right MCA (1.22 %/mmHg)
- Normal VMR of the left MCA (4.54 %/mmHg)
Diamox test (acetazolamide test)

- Patient cooperation is not required in this test
- Acetazolamide leads to vasodilatation of resistance vessels
- 1 g acetazolamide is injected i.v. over 5 minutes
- max. effect on CBF is manifested with an average latency of 10 min. after injection

\[
\frac{F_{V\text{ace}} - F_{V\text{rest}}}{F_{V\text{rest}}} \times 100\% = \text{VMR}
\]

- normal values: VMR 40 %
- pathological limit (mean value - 2SD): VMR 10 %
- side effects: vertigo, oral dysesthesias, in some patients hyper-ventilation with hypocapnia (may completely neutralize its effect)
- disadvantage: acetazolamide cannot give any further information about the vasoconstrictive capabilities of the cerebral vasculature
FV change of right MCA after acetazolamide injection in a young volunteer. Max. FV increase of 53.1 %.
Patients with ICA occlusion (n=452)

Patients with exhausted VMR:
⇒ 50% of these pat. suffered acute stroke

Patients with reduced VMR:
⇒ 28% of these pat. suffered acute stroke

Patients with normal VMR:
⇒ 18% of these pat. suffered acute stroke

[Widder et al.]
MCA FV, ICP, BP, pCO\textsubscript{2} were measured simultaneously in 40 patients with severe intracranial hemorrhage.

Assessment of CO\textsubscript{2} reactivity → initial pCO\textsubscript{2} of each patient was lowered by at least 6 mmHg by controlled hyperventilation.

A significant reduced relative CO\textsubscript{2} reactivity was observed in the patients compared with the controls.

[Klingelhöfer et al.]
Close relationship between relative CO$_2$ reactivity and ICP ($r = -0.89$, $p < 0.0001$).
• Relationship between relative CO$_2$ reactivity and outcome according to GOSS

<table>
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<tr>
<th>GR: good recovery</th>
<th>MD: moderate disability</th>
<th>SD: severe disability</th>
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<tr>
<td>PVS/DEAD: persistent vegetative state/dead</td>
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• Clinical outcome (3 months postinjury) was significantly related to the initial relative CO$_2$ reactivity
Functional TCD during Cognitive Testing

during resting phase

during neuronal activity
P2-PCA supplies almost exclusively the visual cortex.

Therefore, PCA monitoring during visual stimulation enables to study functionally evoked FV response.
The sensitiveness of the P2-PCA reflects this record. Already turning on the light in a dark room at first, leads to a noticeable FV increase.

Simple test to identify the P2-segment of the PCA.
Aaslid studied the visually evoked FV response using a simple on-off light stimulus. He found an average FV increase of 16.4% in the PCAs.

Simple light stimuli generally lead to a significant FV increase:
- Kessler et al. (1993): 20.9 ± 6.2%
- v. Maravic et al. (1992): 24.4 ± 7.2%
- Sitzer et al. (1992): 16.3%

Aaslid, Stroke (1987)
Relationship between complexity of stimulus and FV response.

FV increased to a maximum of 38.8 ± 6.5% with increased complexity of stimulus.

Klingelhöfer et al., Exp Brain Res (1989)
Cerebral Autoregulation

Over a wide range of systemic BP the mechanism of autoregulation minimizes deviations of CBF and protects the capillary bed from nonphysiological pressure and perfusion (e.g. important in the compensation of orthostatic changes).

\[ \text{CBF} = \frac{\text{ABP}}{\text{CVR}} \]
Lower limit of CBF autoregulation in humans. Metaanalysis of 8 studies

Upper limit of CBF autoregulation in experimental renovascular hypertension in the baboon
(Strandgaard et al., Circ. Res 1975)
Cerebral Autoregulation

during resting phase

during blood pressure decrease
Due to the high time resolution of TCD it has now become possible to assess not only static but also dynamic autoregulation.

- The classic definition of static autoregulation describes the relationship between arterial BP and CBF in a state of equilibrium.

- The concept of dynamic autoregulation assesses the effect of autoregulation during dynamic ABP changes.
There are some possibilities for testing cereb. autoregul. (CA) using TCD (selection):

- **Multimodal monitoring and thigh cuffs test**
  Aaslid et al. Cerebral autoregulation dynamics in humans. Stroke 1989
  Tiecks et al. Comparison of static and dynamic CA by means of changes in BP. Stroke 1995

- **Analysis of induced TCD and blood pressure waves („deep breathing“)**

- **Transfer function (TF) analysis of spontaneous and induced oscillations**
  Reinhard et al. Transfer function analysis for clinical evaluation of dynamic CA. Physiol Meas 2003
  Hilz et al. Reduced CBFV and impaired CA in patients with Fabry disease. J Neurol 2004

- **TF analysis between BP/FV(input) and FV/ICP(outp.) combined with step response**

- **Continuous autoregulation monitoring using signal correlation**

- **Continuous autoregulation monitoring by cross-correlation analysis**

- **TCD recordings and rhythmic handgrip**
  Kwan et al. Dynamic CA using combining TCD and rhythmic handgrip. BP Monitoring 2004

- **Transient hyperaemetic response test**
  Giller CA. A bedside test for CA using TCD. Acta Neurochir 1991
$\Delta \phi = \text{phase shift}$
Assessment of dynamic autoregulation in conscious patients using „deep breathing“ method.

- During deep breathing the ABP signal is superimposed by corresponding respiratory waves, inducing again respiratory waves on the FV-signal.
- State of autoregulation is determined by the phase shift between respiratory waves of ABP and FV.
- Intact autoregulation $\rightarrow$ phase shift angle of up to $90^\circ$.
- A low phase shift between ABP and FV ($<30^\circ$) and a high side difference of FV phases ($>14^\circ$) $\rightarrow$ impaired autoregulation.
- Six breathings / min $\rightarrow$ length of respiratory waves 10 sec.
- Phase shift $\rightarrow$ product of time difference (in sec) with $36^\circ$, because one second corresponds to the tenth of the whole breathing period ($360^\circ$).
Assessment of dynamic autoregulation in conscious and unconscious patients using leg-cuff test.

Upper tracing: Normal MFV response to a step change in ABP with a rapid return to baseline within 10 sec.

Lower tracing: Abnormal response of MFV in patients with impaired autoregulation following head injury.

Two cuffs are inflated above systolic BP for 3 minutes. After step decrease (standardized BP decrease of 20 mmHg) BP remains for about 7-10 sec reduced before gradually returning to its initial level.

RCG: TCD should be recorded from 20 sec before until 40 sec after cuff deflation.

If the interest is focused

• on relative changes of CBF or cerebrovascular resistance → evaluation of MFV,
• on the dynamic behavior of autoregulation → evaluation of SFV and DFV.
FV and BP after cuff release are used to calculate the autoregulation index (ARI)

- ARI reflects the change in CVR/s in relation to BP change.
- If there is no autoregulation, FV follows passively the BP course → ARI = 0.
- According to a computer model 9 other possible responses were calculated based on a stepwise autoregulation improvement. Then, the actual response is examined and the „best fit“ with the model is taken as the ARI.
- Normal mean ARI = 4.8 +/-1.0
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<tr>
<th>Test</th>
<th>Advantage</th>
<th>Restriction</th>
<th>RCG</th>
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<tr>
<td>Induced oscillations (“deep breathing“)</td>
<td>non-invasive</td>
<td>possible influence by change in CO₂</td>
<td>suitable to be applied in awake, cooperative patients</td>
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<td>Cuff Test</td>
<td>robust, simple to perform</td>
<td>semi-invasive, inflation of the cuffs is painful; contraindicat. in pat. with: - deep leg vein thrombosis - clinically relevant heart failure - circulatory lability and critical CPP</td>
<td>suitable to be applied both in awake and unconscious patients at intensive care unit</td>
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<td>Signal Correlation Test</td>
<td>independent of patient’s cooperation; not influenced by patient due to only passive signal analysis; long-term continuous monitoring possible</td>
<td>invasive ICP measurement necessary</td>
<td>suitable to be applied in unconscious patients at intensive care unit; especially in all patients the Cuff Test cannot be applied</td>
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CONCLUSION I

• CO₂/ Diamox test → simple, non-invasive procedure for the assessment of VMR

• Important criterion for the assessment of the collateral capacity of the circle of Willis in ICA stenoses and occlusions

• Important criterion for the indication of carotid re-construction

• ICA occlusion and exhausted VMR → high risk for low-flow infarction

• Modified CO₂ test → early criterion for the assessment of the ”outcome” in patients with severe brain lesions
Conclusion II

• Functionally evoked changes of TCD parameters demonstrate that reactive perfusion patterns are specific to the type of stimuli.

• Functional TCD represents a powerful tool in the detection of rapid regulatory mechanism related to changes in functional neuronal activity.

• Bilateral TCD recordings may offer the possibility of a noninvasive method to study the hemispheric dominance of language.

• The high time resolution of TCD enables to assess not only static but also dynamic autoregulation.